Cost-utility analysis of operative versus non-operative treatment for colorectal liver metastases

Roberts, K. J.; Sutton, Andrew; Prasad, K. R.; Toogood, G. J.; Lodge, J. P. A.

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K. J. Roberts, A. J. Sutton, K. R. Prasad, G. J. Toogood and J. P. A. Lodge

Table S1 Model parameters

	Baseline (%)	Notes
Initial population states		
Operative group		
Survives after resection	95.4 (373 of 391)	Observational data*
Dies following resection	4.6 (18 of 391)	Observational data*
Non-operative group		
Inoperable patients who receive chemotherapy	74 (34 of 46)	Observational data*
Inoperable patients who do not receive chemotherapy	26 (12 of 46)	Observational data*
Postoperative complications among patients who die following resection	83 (15 of 18)	Observational data*
Survivors after resection who postoperative complications	14.6 (49 of 335)	Observational data*
Extrahepatic procedures that are VATS	15 (8 of 52)	Observational data*
Outcome of recurrence		
Hepatic resection	21.3 (64 of 300)	Observational data*
Extrahepatic resection	14.3 (43 of 300)	Observational data*
Non-operable – chemotherapy	47.6 (193 of 300) × (34 of 46)	Observational data*
Non-operable – no chemotherapy	16.8 (193 of 300) × (12 of 46)	Observational data*
Proportion of patients dying after resection/extrahepatic procedure	4.6 (18 of 395)	Observational data*
Diarrhoea	0.7	Levi *et al.*[26]; assume that this proportion of patients receiving chemotherapy suffers diarrhoea at any one time
Neutropenic fever	2.3	Levi *et al.*[26]; assume that this proportion of patients receiving chemotherapy suffers neutropenic fever at any one time

The table shows actual outcomes of the patient cohorts. Among 286 patients in the operative cohort a further 105 operations were performed for recurrent hepatic and extrahepatic disease. *Some patients had more than one procedure. VATS, video-assisted thoracoscopic surgery.

Table S2 Transition probabilities used in the Markov model at baseline

	Baseline (probability per week)	Notes
Mortality rate among patients receiving chemotherapy	0.0092 (0.0061)	Kaplan–Meier with Greenwood's formula used to obtain s.e.
Mortality rate among those who die as a result of liver resection/extrahepatic procedure	0.5527 (0.3336)	Assume that death rates for extrahepatic and resection procedures are the same
Mortality rate among inoperable patients	0.0190 (0.0182)	Kaplan–Meier with Greenwood's formula used to obtain s.e.
Recurrence rate	0.001 (0.00008)	Kaplan–Meier with Greenwood's formula used to obtain s.e.
Mortality rate among patients in resection group	0.0022 (0.0002)	Kaplan–Meier with Greenwood's formula used to obtain s.e.

Values in parentheses are s.e.

Table S3 Utility values used in the Markov model

	Base-case estimate	SA values	Source
Utility after liver resection without morbidity/ mortality during hospitalization postop.	0.60	±0.06	van Dam *et al.*[28]. SA value assumed to be within 10% of base-case estimate
Utility after liver resection without morbidity/ mortality 3 months postop.	0.74	±0.074	van Dam *et al.*[28]. SA value assumed to be within 10% of base-case estimate
Utility after liver resection without morbidity/ mortality 6 months postop.	0.80	±0.08	van Dam *et al.*[28]. SA value assumed to be within 10% of base-case estimate
Utility after liver resection with morbidity during hospitalization postop.	0.57	±0.057	van Dam *et al.*[28]. SA value assumed to be within 10% of base-case estimate
Utility after liver resection with morbidity 3 months postop.	0.71	±0.071	van Dam *et al.*[28]. SA value assumed to be within 10% of base-case estimate
Utility after liver resection with morbidity 6 months postop.	0.78	±0.078	van Dam *et al.*[28]. SA value assumed to be within 10% of base-case estimate
Utility ≥ 1 year postop. (both liver resection and extrahepatic procedure)	0.83	Range 0.17–1.00	Tanis *et al.*[29]
Extrahepatic procedure during hospitalization postop.	0.6	±0.06	Assumed to be the same as resection
Extrahepatic procedure – VATS 3 months postop.	0.73	s.d. 0.18	Iwahashi *et al.*[30]
Extrahepatic procedure – VATS 6 months postop.	0.75	s.d. 0.19	Iwahashi *et al.*[30]
Extrahepatic procedure – non-VATS 3 months postop.	0.72	s.d. 0.25	Iwahashi *et al.*[30]
Extrahepatic procedure – non-VATS 6 months postop.	0.77	s.d. 0.24	Iwahashi *et al.*[30]
Utility during chemotherapy	0.68	Plausible range 0.54–0.82	Levi *et al.*[26]
Neutropenic fever (2.3%)	0.47	Plausible range 0.38–0.56	Levi *et al.*[26]
Grade 3–4 diarrhoea (0.7%)	0.32	Plausible range 0.26–0.38	Levi *et al.*[26]
Inoperable (palliative treatments)	0.63	Plausible range 0.50–0.76	Levi *et al.*[26]

SA, sensitivity analysis; VATS, video-assisted thoracoscopic surgery.

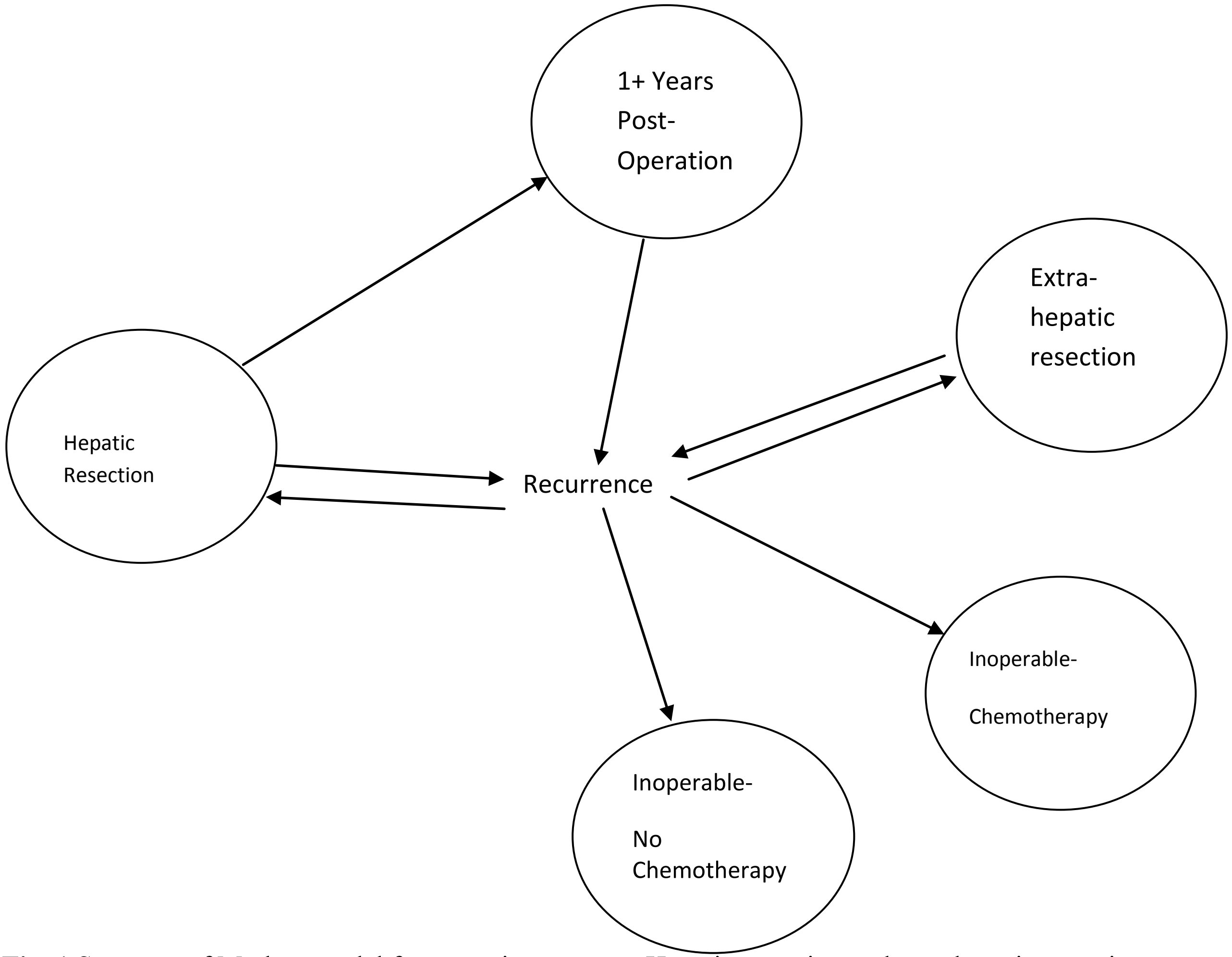


Fig. 1 Structure of Markov model for operative strategy. Hepatic resection and extrahepatic resection states were further stratified into hospitalized (live and die), within 6 months postop. and within 12 months postop., with these states subdivided into with or without complications. All model states are subject to colorectal cancer-related and background mortality. Recurrence is an event rather than a model state

Table S4 Distributions used in the probabilistic sensitivity analysis

	Distribution	a	b
Proportion of inoperable patients who receive chemotherapy	Beta	46	34
Proportion of those who die following a resection and have complications	Beta	18	3
Proportion of those who live following a resection and have complications	Beta	335	49
CT scans per week for patients following the inoperable strategy	Beta	625	29
Outpatient appointments per week for patients following the inoperable strategy	Beta	625	187
MRI scans per week for patients following inoperable strategy	Beta	625	7
Proportion of extrahepatic procedures that are VATS	Beta	52	8
Proportion who die following a resection or extrahepatic procedure	Beta	395	18
Probability of recurrence among patients following the operable strategy	Beta	224.73	1887050.3
Probability of disease-related mortality for patients on chemotherapy	Beta	2.24	242.10
Weekly probability of death among patients who die following an extrahepatic procedure (informs hospital stay until death)	Beta	1.23	0.99
Weekly probability of leaving hospital following extrahepatic procedures and resection (informs postop. hospital stay)	Beta	3.90	4.12
Probability of disease-related mortality for those inoperable not receiving chemotherapy	Beta	1.07	55.29
Probability of disease-related mortality among patients following operable strategy	Beta	93.73	42247.17
Proportion of patients with postop. neutropenic fever	Beta	0.98	41.50
Proportion of patients with postop. diarrhoea	Beta	258.41	549.12
Utility among inoperable patients who do not receive chemotherapy	Beta	637.93	374.66
Utility among patients receiving chemotherapy	Beta	428.11	201.46
Utility during postop. inpatient stay without complications	Beta	235.81	157
Utility during postop. inpatient stay with complications	Beta	211.65	159.60
Utility for patients 3 months after extrahepatic procedure with VATS	Beta	4.44	1.64
Utility for patients 6 months after extrahepatic procedure with VATS	Beta	3.90	1.30
Utility for patients 3 months after non-VATS extrahepatic procedure	Beta	2.32	0.90
Utility for patients 6 months after non-VATS extrahepatic procedure	Beta	2.37	0.71
Utility for patients 3 months after resection, no complications	Beta	163.92	57.46
Utility for patients 6 months after resection, no complications	Beta	140.28	34.93
Utility for patients 3 months after resection, complications	Beta	123.43	50.40
Utility for patients 6 months after resection, complications	Beta	129.02	36.37
Utility for patients > 1 year after procedure	Beta	9.76	2
Utility for patients with neutropenic fever	Beta	516.23	582.13
Utility for patients with diarrhoea	Beta	258.41	549.12
Cost of chemotherapy (weekly) (€)	Normal	Mean 430	s.e. 64.79
Cost of postresection hospital stay (variation due to different initial procedure being implemented) (€)	Normal	Mean 2886.61	s.e. 24.65
Cost of resection procedure (€)	Normal	Mean 7132.12	s.e. 93.78

Two parameters are used to describe the beta distribution, a and b. The beta (a, b) distribution can be used to precisely represent uncertainly in a proportion when the only available information is the number of positive cases (a) and negative cases (b). In this study, where exact numbers were available, these were used to inform the parameters of each beta distribution. Where only mean and s.e. values were available, the method of moments was used to estimate a and b. VATS, video-assisted thoracoscopic surgery.

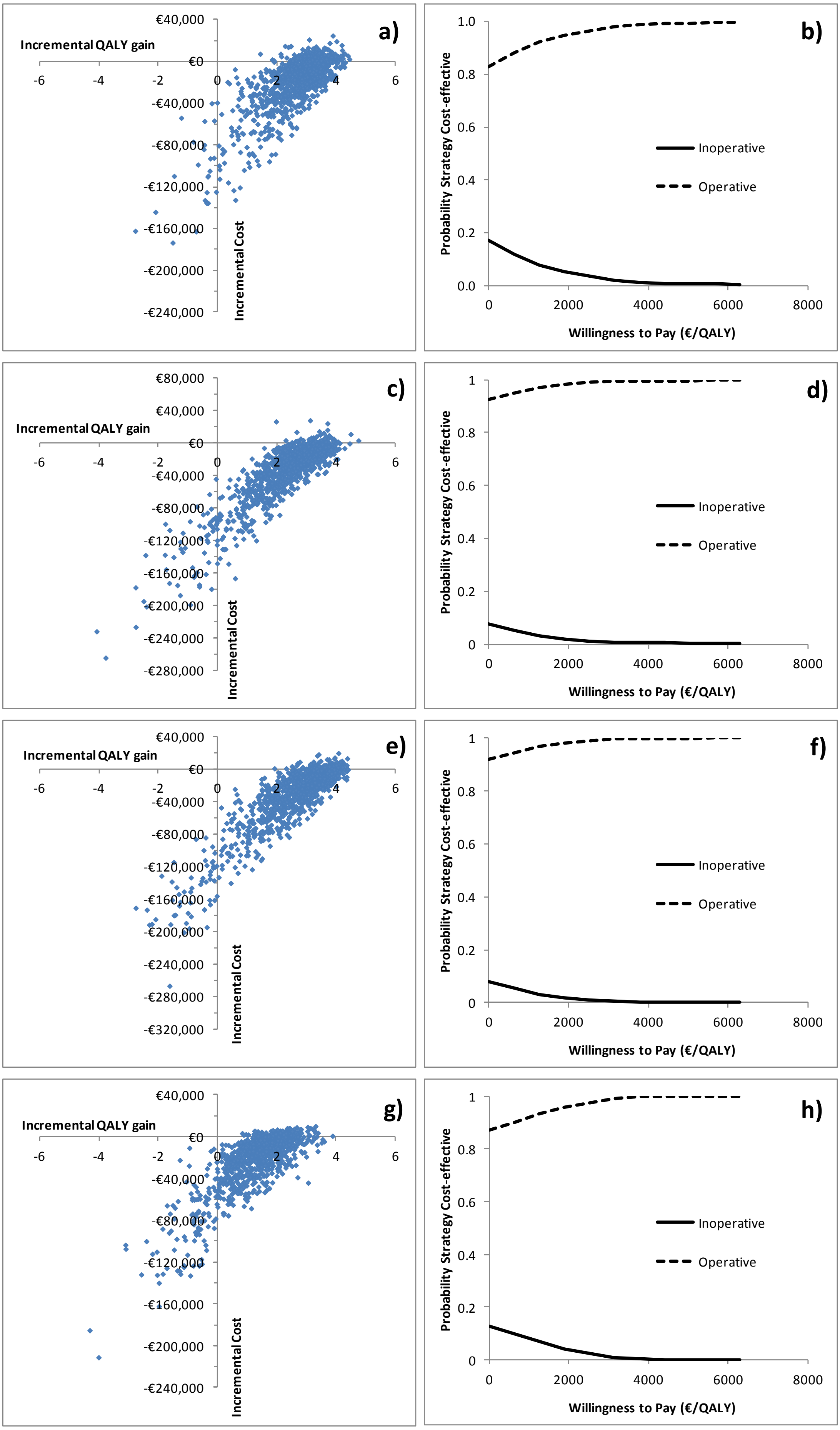
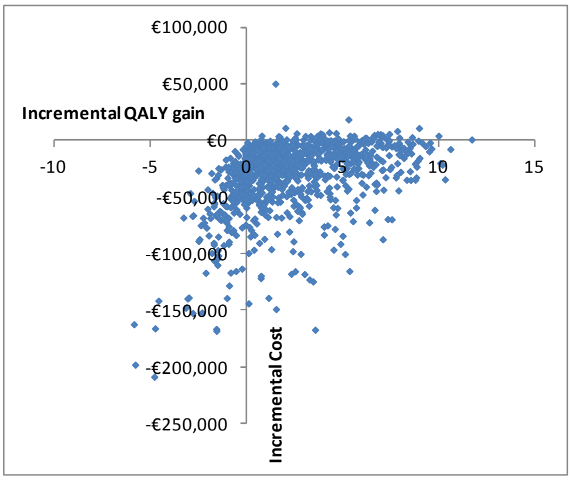

a)
Incremental QALY gain
Incremental Cost
€40,000
€0
-€40,000
-€80,000
-€120,000
-€160,000
-€200,000
-€240,000
-6
-4
-2
0
2
4
6
b)
Probability Strategy Cost-effective
Willingness to Pay (€/QALY)
Inoperative
Operative
1.0
0.8
0.6
0.4
0.2
0.0
0
2000
4000
6000
8000
c)
Incremental QALY gain
Incremental Cost
€80,000
€40,000
€0
-€40,000
-€80,000
-€120,000
-€160,000
-€200,000
-€240,000
-€280,000
d)
Probability Strategy Cost-effective
Willingness to Pay (€/QALY)
Inoperative
Operative
e)
Incremental QALY gain
Incremental Cost
€40,000
€0
-€40,000
-€80,000
-€120,000
-€160,000
-€200,000
-€240,000
-€280,000
-€320,000
f)
Probability Strategy Cost-effective
Willingness to Pay (€/QALY)
Inoperative
Operative
g)
Incremental QALY gain
Incremental Cost
€40,000
€0
-€40,000
-€80,000
-€120,000
-€160,000
-€200,000
-€240,000
h)
Probability Strategy Cost-effective
Willingness to Pay (€/QALY)
Inoperative
Operative

Fig. S2 Scatter plots and cost-effectiveness acceptability curves for the probabilistic sensitivity analysis, assuming that: **a**,**b** there are no postoperative deaths following initial resection in the operative pathway; **c**,**d** all patients in the non-operative pathway receive chemotherapy; **e**,**f** there are no postoperative deaths following initial resection in the operative pathway and all patients in the non-operative pathway receive chemotherapy; and **g**,**h** all patients in the operative pathway have involved surgical margins (all patients with clear (R0) resection margins were excluded from analyses). In all these examples it can be seen that the conclusions drawn from the model are robust and that the operative strategy is certain to be the most cost-effective option for a willingness-to-pay (WTP) for 1 quality-adjusted life-year (QALY) of €6000 or more



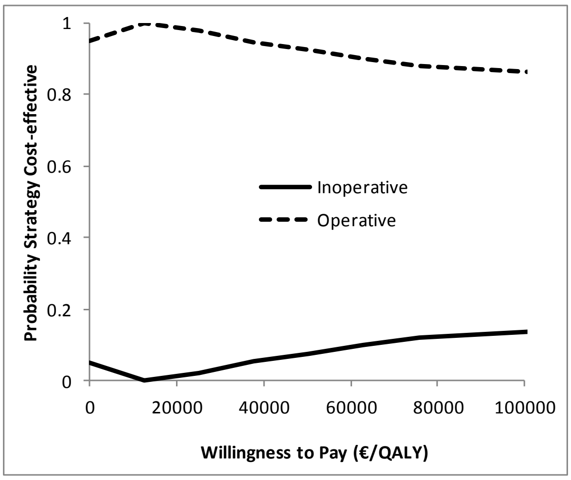


Fig. S3 Scatter plot and cost-effectiveness acceptability curve for the probabilistic sensitivity analysis assuming that there were no survivors at 10 years in the operative pathway. For a willingness-to-pay (WTP) for 1 quality-adjusted life-year (QALY) of less than €50 000, the operative strategy is still more than 90 per cent likely to be the most cost-effective strategy, and more than 80 per cent likely to be cost-effective for a WTP of up to €100 000 per QALY (steady state value 79.4 per cent)